CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074596

Trade Name : ACYCLOVIR SODIUM FOR INJECTION

Generic Name: Acyclovir Sodium for Injection

Sponsor : Bedford Laboratories

Approval Date: March 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074596

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074596

APPROVAL LETTER

ANDA 74-596

Bedford Laboratories™
Attention: Robert V. Kasubick, Ph.D.
Division of Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146

Dear Dr. Kasubick:

This is in reference to your abbreviated new drug application dated December 22, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Sodium for Injection, 500 mg base/vial and 1 g base/vial.

Reference is also made to your amendment dated January 27, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Sodium for Injection, 500 mg base/vial and 1 g base/vial to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Sterile Powder, 500 mg base/vial and 1 g base/vial of Glaxo Wellcome Inc.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[redacted]

Douglas L. Sporn 7-22-97
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074596

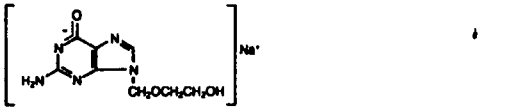
FINAL PRINTED LABELING

ACYCLOVIR SODIUM FOR INJECTION FOR INTRAVENOUS INFUSION ONLY

DESCRIPTION

Acyclovir is an antiviral drug active against herpesviruses. Acyclovir sodium for injection is a formulation for intravenous administration. Each 5.49 mg of sterile lyophilized acyclovir sodium is equivalent to 5 mg acyclovir.

The chemical name of acyclovir sodium is 9-[(2-Hydroxyethoxy)methyl]guanine sodium salt; it has the following structural formula:



Molecular Formula: $C_8H_{10}N_5O_3Na$

Acyclovir sodium is a white, crystalline powder with a molecular weight of 247.19, and a solubility in water exceeding 100 mg/mL. Each 500 mg or 1000 mg vial of Acyclovir sodium for injection when reconstituted with 10 mL or 20 mL, respectively, sterile diluent yields 50 mg/mL acyclovir (pH approximately 11). Further dilution in any appropriate intravenous solution must be performed before infusion (see Method of Preparation). At physiologic pH, acyclovir exists as the un-ionized form with a molecular weight of 225.21 and a maximum solubility of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with Herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Mikrobiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex virus to acyclovir and the clinical response to therapy has not been established in man, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 - 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population.

Most of the less sensitive clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.8 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir has been evaluated in 95 patients (9 studies). Results were obtained in adult patients with normal renal function during Phase 1/2 studies after single doses ranging from 0.5 to 15 mg/kg and after multiple doses ranging from 2.5 to 15 mg/kg every 8 hours. Pharmacokinetics was also determined in pediatric patients with normal renal function ranging in age from 1 to 17 years at doses of 250 mg/m² or 500 mg/m² every 8 hours. In these studies, dose-independent pharmacokinetics is observed in the range of 0.5 to 15 mg/kg. Proportionality between dose and plasma levels is seen after single doses or at steady state after multiple dosing.[23] When acyclovir was administered to adults at 5 mg/kg (approximately 250 mg/m²) by 1 hour infusions every 8 hours, mean steady-state peak and trough concentrations of 9.8 mcg/mL (5.5 to 13.8 mcg/mL) and 0.7 mcg/mL (0.2 to 1.9 mcg/mL), respectively, were achieved. Similar concentrations are achieved in children over 1 year of age when doses of 250 mg/m² are given by 1 hour infusions every 8 hours. At a dose to 10 mg/kg given by 1 hour infusion every 8 hours, mean steady-state peak and trough concentrations were 22.9 mcg/mL (14.1 to 44.1 mcg/mL) and 1.9 mcg/mL (0.5 to 2.9 mcg/mL). Similar concentrations were achieved in children dosed at 500 mg/m² given by 1 hour infusion every 8 hours. Concentrations achieved in the cerebrospinal fluid are approximately 50% of plasma values. Plasma protein binding is relatively low (9% to 33%) and drug interactions involving binding site displacement are not anticipated.[23]

Renal excretion of unchanged drug by glomerular filtration and tubular secretion is the major route of acyclovir elimination accounting for 62% to 91% of the dose as determined by ^{14}C-labeled drug. The only major urinary metabolite detected is 9-carboxyethoxymethylguanine. This may account for up to 14.1% of the dose in patients with normal renal function. An insignificant amount of drug is recovered in feces and expired CO_2 and there is no evidence to suggest tissue retention.[23] However, postmortem examinations have shown that acyclovir is widely distributed in tissues and body fluids including brain, kidney, lung, liver, muscle, spleen, uterus, vaginal mucosa, vaginal secretions, cerebrospinal fluid, and herpetic vesicular fluid.

The half-life and total body clearance of acyclovir is dependent on renal function as shown below.[23]

Creatinine Clearance (mL/min/1.73 m²)	Half-Life (hr)	Total Body Clearance (mL/min/1.73 m²)
>80	2.5	327
50 - 80	3.0	248
15 - 50	3.5	190
0 (Anuric)	19.5	29

Acyclovir was administered at a dose of 2.5 mg/kg to 6 adult patients with severe renal failure. The peak and trough plasma levels during the 47 hours preceding hemodialysis were 8.5 mcg/mL and 0.7 mcg/mL, respectively.[24,25]

Consult **DOSAGE AND ADMINISTRATION** section for recommended adjustments in dosing based upon creatinine clearance.

The half-life and total body clearance of acyclovir in pediatric patients over 1 year of age is similar to those in adults with normal renal function (see **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND USAGE

Acyclovir sodium for injection is indicated for the treatment of initial and recurrent mucosal and cutaneous Herpes simplex (HSV-1 and HSV-2) and varicella-zoster (shingles) infections in immunocompromised patients. It is also indicated for herpes simplex encephalitis in patients over 6 months of age and for severe initial clinical episodes of herpes genitalis in patients who are not immunocompromised.

Herpes Simplex Infections in Immunocompromised Patients
A multicenter trial of intravenous acyclovir at a dose of 250 mg/m² every 8 hours (750 mg/m²/day) for 7 days was conducted in 98 immunocompromised patients (73 adults and 25 children) with oro-facial, esophageal, genital, and other localized infections (52 treated with acyclovir and 46 with placebo). Acyclovir significantly decreased virus excretion, reduced pain, and promoted scabbing and rapid healing of lesions.[14,26,27,28]

Initial Episodes of Herpes Genitalis
In placebo-controlled trials, 58 patients with initial genital herpes were treated with intravenous acyclovir 5 mg/kg or placebo (27 patients treated with acyclovir and 31 treated with placebo) every eight hours for 5 days. Acyclovir decreased the duration of viral excretion, new lesion formation, and duration of vesicles and promoted healing of lesions.[26,29,30]

Herpes Simplex Encephalitis
Sixty-two patients ages 6 months to 79 years with brain biopsy-proven herpes simplex encephalitis were randomized to receive either acyclovir (30 mg/kg/day) or adenine arabinoside (15 mg/kg/day) for 10 days (28 were treated with acyclovir and 34 with adenine arabinoside).[31] Overall mortality for acyclovir recipients at 6 months was 18% compared to 59% for adenine arabinoside recipients ($P = 0.003$). The proportion of acyclovir recipients functioning normally or with only mild sequelae (e.g., decreased attention span) was 39% compared to 9% of adenine arabinoside recipients ($P = 0.01$). The remaining patients in both groups had moderate (e.g., hemiparesis, speech impediment or seizure) or severe (continuous supportive care required) neurologic sequelae.

After 12 months of follow-up, two additional acyclovir recipients had died, resulting in an overall mortality of 25% compared to 59% for adenine arabinoside recipients ($P = 0.02$). Morbidity assessments at that time indicated that 32% of acyclovir recipients were functioning normally, or with only mild sequelae compared to 12% adenine arabinoside patients ($P = 0.06$). Moderate to severe impairment was noted in all remaining patients in both groups who were available for evaluation. Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with acyclovir treatment. An additional controlled study performed in Europe[32] demonstrated similar findings. The superiority of acyclovir over adenine arabinoside for neonatal herpes encephalitis has not been demonstrated.

Varicella-Zoster Infections in Immunocompromised Patients
A multicenter trial of intravenous acyclovir at a dose of 500 mg/m² every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir halted progression of infection as determined by significant reductions in cutaneous dissemination, visceral dissemination, or the proportion of patients deemed treatment failures.[26,33]

A comparative trial of acyclovir and vidarabine was conducted in 22 severely immunocompromised patients with zoster infections. Acyclovir was shown to be superior to vidarabine as demonstrated by significant differences in the time of new lesion formation, the time to pain reduction, the time to lesion crusting, the time to complete healing, the incidence of fever and the duration of positive viral cultures. In addition, cutaneous dissemination occurred in none of the 10 acyclovir recipients compared to 5 of the 10 vidarabine recipients who presented with localized dermatomal disease.[34]

Diagnosis
Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions associated with Herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[35]

The Tzanck smear does not distinguish varicella-zos

Herpes encephalitis should be confirmed by brain t
causes of neurologic disease. A presumptive diagno
visualized with various diagnostic methods includi
troencephalography. Culture of the cerebrospinal fl

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(see **PRECAUTIONS** and **DOSAGE AND ADMINISTR**

General: The recommended dosage, frequency, an

Although the aqueous solubility of acyclovir sodium
if the maximum solubility of free acyclovir (2.5 mg
complication causes a rise in serum creatinine and
tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clea
patient's hydration, other treatments, and the rate of
dysfunction, while in controlled studies, infusion of
lower frequency - 3.8%. Concomitant use of other
ment with acyclovir more likely. In most instances
ment of water and electrolyte balance, drug dosage
changes may progress to acute renal failure.

Administration of acyclovir by intravenous infusion
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to prevent precipitation in renal tubules. Recomme
recommended hydration should be balanced by the

When dosage adjustments are required they should

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Drug Interactions: Co-administration of probenec
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Carcinogenesis, Mutagenesis, Impairment of Fer
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After 12 months of follow-up, two additional acyclovir recipients had died, resulting in an overall mortality of 25% compared to 59% for adenine arabinoside recipients ($P = 0.02$). Morbidity assessments at that time indicated that 32% of acyclovir recipients were functioning normally, or with only mild sequelae compared to 12% adenine arabinoside patients ($P = 0.06$). Moderate to severe impairment was noted in all remaining patients in both groups who were available for evaluation. Patients less than 30 years of age and those who had the least severe neurologic involvement at time of entry into study had the best outcome with acyclovir treatment. An additional controlled study performed in Europe[32] demonstrated similar findings. The superiority of acyclovir over adenine arabinoside for neonatal herpes encephalitis has not been demonstrated.

Varicella-Zoster Infections in Immunocompromised Patients

A multicenter trial of intravenous acyclovir at a dose of 500 mg/m^2 every 8 hours for 7 days was conducted in immunocompromised patients with zoster infections (shingles). Ninety-four (94) patients were evaluated (52 patients were treated with acyclovir and 42 with placebo). Acyclovir halted progression of infection as determined by significant reductions in cutaneous dissemination, visceral dissemination, or the proportion of patients deemed treatment failures.[28,33]

A comparative trial of acyclovir and vidarabine was conducted in 22 severely immunocompromised patients with zoster infections. Acyclovir was shown to be superior to vidarabine as demonstrated by significant differences in the time of new lesion formation, the time to pain reduction, the time to lesion crusting, the time to complete healing, the incidence of fever and the duration of positive viral cultures. In addition, cutaneous dissemination occurred in none of the 16 acyclovir recipients compared to 5 of the 10 vidarabine recipients who presented with localized dermatomal disease.[34]

Diagnosis

Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. In initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. Whereas cutaneous lesions associated with Herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may assist in the diagnosis.[35]

The Tzanck smear does not distinguish varicella-zoster from herpes simplex infections. Culture of varicella-zoster is not widely available.

Herpes encephalitis should be confirmed by brain biopsy to obtain tissue for histologic examination and viral culture and to exclude other causes of neurologic disease. A presumptive diagnosis of herpes encephalitis may be made on the basis of focal changes in the temporal lobe visualized with various diagnostic methods including magnetic resonance imaging, computerized tomography, radionuclide scans or electroencephalography. Culture of the cerebrospinal fluid for herpes simplex virus is unreliable.

CONTRAINDICATIONS

Acyclovir sodium for injection is contraindicated for patients who develop hypersensitivity to the drug.

WARNINGS

Acyclovir sodium for injection is intended for intravenous infusion only, and should not be administered topically, intramuscularly, orally, subcutaneously, or in the eye. Intravenous infusions must be given over a period of at least 1 (one) hour to reduce the risk of renal tubular damage (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

PRECAUTIONS

General: The recommended dosage, frequency, and length of treatment should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Although the aqueous solubility of acyclovir sodium (for infusion) is > 100 mg/mL, precipitation of acyclovir crystals in renal tubules can occur if the maximum solubility of free acyclovir (2.5 mg/mL at 37° C in water) is exceeded or if the drug is administered by bolus injection. This complication causes a rise in serum creatinine and blood urea nitrogen (BUN), and a decrease in renal creatinine clearance. Ensuing renal tubular damage can produce acute renal failure.

Abnormal renal function (decreased creatinine clearance) can occur as a result of acyclovir administration and depends on the state of the patient's hydration, other treatments, and the rate of drug administration. Bolus administration of the drug leads to a 10% incidence of renal dysfunction, while in controlled studies, infusion of 5 mg/kg (250 mg/m^2) and 10 mg/kg (500 mg/m^2) over an hour was associated with a lower frequency - 3.6%. Concomitant use of other nephrotoxic drugs, pre-existing renal disease, and dehydration make further renal impairment with acyclovir more likely. In most instances, alterations of renal function were transient and resolved spontaneously or with improvement of water and electrolyte balance, drug dosage adjustment or discontinuation of drug administration. However, in some instances, these changes may progress to acute renal failure.

Administration of acyclovir by intravenous infusion must be accompanied by adequate hydration. Since maximum urine concentration occurs within the first 2 hours following infusion, particular attention should be given to establishing sufficient urine flow during that period in order to prevent precipitation in renal tubules. Recommended urine output is ≥ 500 mL per gram of drug infused. In patients with encephalitis, the recommended hydration should be balanced by the risk of cerebral edema.

When dosage adjustments are required they should be based on estimated creatinine clearance (see **DOSAGE AND ADMINISTRATION**).

Approximately 1% of patients receiving intravenous acyclovir have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma. Acyclovir should be used with caution in those patients who have underlying neurologic abnormalities and those with serious renal, hepatic, or electrolyte abnormalities or significant hypoxia. It should also be used with caution in patients who have manifested prior neurologic reactions to cytotoxic drugs or those receiving concomitant intrathecal methotrexate or interferon.

Exposure of HSV isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. These viruses usually are deficient in thymidine kinase (required for acyclovir activation) and are less pathogenic in animals. Similar isolates have been observed in severely immunocompromised patients during the course of controlled and uncontrolled studies of intravenously administered acyclovir. These occurred in patients with severe combined immunodeficiencies or following bone marrow transplantation. The presence of these viruses was not associated with a worsening of clinical illness and, in some instances, the virus disappeared spontaneously. The possibility of the appearance of less sensitive viruses must be recognized when treating such patients.[11-19] The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has not been established.

Drug Interactions: Co-administration of probenecid with acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[36] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady state plasma acyclovir concentrations observed in humans treated with 30 mg/kg/day (10 mg/kg/every 8 hr, dosing appropriate for treatment of herpes zoster or herpes encephalitis), or 15 mg/kg/day (5 mg/kg/every 8 hr, dosing appropriate for treatment of primary genital herpes or herpes simplex infections in immunocompromised patients). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations in both the mouse and rat bioassay were lower than concentrations in humans.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (3 to 5 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (3 to 6 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (5 to 10 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (31 and 61 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (3 and 6 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 13 to 25 times the acyclovir plasma levels achieved in man. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 20 to 40 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 150 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 120 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study plasma levels were the same as human levels. At 50 mg/kg/day, s.c. in the rat (1 to 2 times human levels), there was a statistically significant increase in post-implantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (1 to 3 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (4 to 9 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day, s.c. (1 to 2 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F_1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (4 to 9 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the one-month study and were 2 to 4 times human levels in the six-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days post-dose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day, plasma levels were 4 to 8 times human levels, while at 200 mg/kg/day they were 13 to 25 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (2 to 3 times human levels) and in dogs given 80 mg/kg/day orally for one year (the same as human levels).

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels the same as, 4 and 8, and 1 and 2 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[37] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 5 and 10 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[38,39] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

ADVERSE REACTIONS

The adverse reactions listed below have been observed in controlled and uncontrolled clinical trials in approximately 700 patients who received acyclovir at ~ 5 mg/kg (250 mg/m²) three times daily, and approximately 300 patients who received ~ 10 mg/kg (500 mg/m²) three times daily.

The most frequent adverse reactions reported during administration of acyclovir were inflammation or phlebitis at the injection site in approximately 9% of the patients, and transient elevations of serum creatinine or BUN in 5% to 10% (the higher incidence occurred usually following rapid [less than 10 minutes] intravenous infusion). Nausea and/or vomiting occurred in approximately 7% of the patients (the majority occurring in nonhospitalized patients who received 10 mg/kg). Itching, rash or hives occurred in approximately 2% of patients. Elevation of transaminases occurred in 1% to 2% of patients.

Approximately 1% of patients receiving intravenous acyclovir sodium have manifested encephalopathic changes characterized by either lethargy, obtundation, tremors, confusion, hallucinations, agitation, seizures or coma (see **PRECAUTIONS**).

Adverse reactions which occurred at a frequency of less than 1% and which were probably or possibly related to intravenous administration of acyclovir were: anemia, anuria, hematuria, hypotension, edema, anorexia, lightheadedness, thirst, headache, diaphoresis, fever, neutropenia, thrombocytopenia, abnormal urinalysis (characterized by an increase in formed elements in urine sediment), and pain on urination.

Other reactions have been reported with a frequency of less than 1% in patients receiving acyclovir sodium, but a causal relationship between acyclovir and the reaction could not be determined. These include pulmonary edema with cardiac tamponade, abdominal pain, chest pain, thrombocytosis, leukocytosis, neutrophilia, ischemia of digits, hypokalemia, purpura fulminans, pressure on urination, hemoglobinemia and rigors.

Observed During Clinical Practice: Based on clinical practice experience in patients treated with intravenous acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, pain, and rarely, anaphylaxis
Skin: rash
Digestive: elevated liver function tests, nausea
Urogenital: elevated blood urea nitrogen, elevated creatinine, renal failure
Hemic and Lymphatic: leukopenia
Nervous: agitation, coma, confusion, convulsions, delirium, hallucinations, obtundation, psychosis

OVERDOSAGE

Overdosage has been reported following administration of bolus injections, or inappropriately high doses, and in patients whose fluid and electrolyte balance was not properly monitored. This has resulted in elevations in BUN, serum creatinine, and subsequent renal failure. Lethargy, convulsions, and coma have been reported rarely.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded (see **PRECAUTIONS**). Renal lesions related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. In the event of overdosage, sufficient urine flow must be maintained to prevent precipitation of drug in renal tubules. Recommended urine output is ≥ 500 mL per gram of drug infused. A six-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

CAUTION - RAPID OR BOLUS INTRAVENOUS AND INTRAMUSCULAR OR SUBCUTANEOUS INJECTION MUST BE AVOIDED. Therapy should be initiated as early as possible following onset of signs and symptoms. For diagnosis - see INDICATIONS.

Dosage:

HERPES SIMPLEX INFECTIONS

MUCOSAL AND CUTANEOUS HERPES SIMPLEX (HSV-1 and HSV-2) INFECTIONS IN IMMUNOCOMPROMISED PATIENTS - 5 mg/kg infused at a constant rate over 1 hour, every 8 hours (15 mg/kg/day) for 7 days in adult patients with normal renal function. In children under 12 years of age, more accurate dosing can be attained by infusing 250 mg/m² at a constant rate over 1 hour, every 8 hours (750 mg/m²/day) for 7 days.

SEVERE INITIAL CLINICAL EPISODES OF HERPES GENITALIS - The same dose given above - administered for 5 days.

HERPES SIMPLEX ENCEPHALITIS - 10 mg/kg infused at a constant rate over at least 1 hour, every 8 hours for 10 days. In children between 6 months and 12 years of age, more accurate dosing is achieved by infusing 500 mg/m², at a constant rate over at least one hour, every 8 hours for 10 days.

VARICELLA ZOSTER INFECTIONS

ZOSTER IN IMMUNOCOMPROMISED PATIENTS - 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days in adult patients with normal renal function. In children under 12 years of age, equivalent plasma concentrations are attained by infusing 500 mg/m² at a constant rate over at least 1 hour, every 8 hours for 7 days. Obese patients should be dosed at 10 mg/kg (Ideal Body Weight). A maximum dose equivalent to 500 mg/m² every 8 hours should not be exceeded for any patient.

PATIENTS WITH ACUTE OR CHRONIC RENAL IMPAIRMENT: Refer to **DOSAGE AND ADMINISTRATION** section for recommended doses, and adjust the dosing interval as indicated in the table below.

Creatinine Clearance (mL/min/1.73 m²)	Percent of Recommended Dose	Dosing Interval (hours)
> 50	100%	8
25 - 50	100%	12
10 -25	100%	24
0 - 10	50%	24

Hemodialysis: For patients who require dialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[24,25]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[40,41]

Method of Preparation: Each 10 mL vial contains acyclovir sodium equivalent to 500 mg of acyclovir. Each 20 mL vial contains acyclovir sodium equivalent to 1000 mg of acyclovir. The contents of the vial should be dissolved in Sterile Water for Injection as follows:

Contents of Vial	Amount of Diluent
500 mg	10 mL
1000 mg	20 mL

The resulting solution in each case contains 50 mg acyclovir per mL (pH approximately 11). Shake the vial well to assure complete dissolution before measuring and transferring each individual dose. DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.

Administration: The calculated dose should then be removed and added to any appropriate intravenous solution at a volume selected for administration during each 1 hour infusion. Infusion concentrations of approximately 7 mg/mL or lower are recommended. In clinical studies, the average 70 kg adult received between 80 and 150 mL of fluid per dose. Higher concentrations (e.g., 10 mg/mL) may produce phlebitis or inflammation at the injection site upon inadvertent extravasation. Standard, commercially available electrolyte and glucose solutions are suitable for intravenous administration; biologic or colloidal fluids (e.g., blood products, protein solutions, etc.) are not recommended.

Once in solution in the vial at a concentration of 50 mg/mL, the drug should be used within 12 hours. Once diluted for administration, each dose should be used within 24 hours. Refrigeration of reconstituted solutions may result in formation of a precipitate which will redissolve at room temperature.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Acyclovir Sodium for Injection is available as:

10 mL sterile vials, each containing acyclovir sodium equivalent to 500 mg of acyclovir, carton of 10. (**NDC 55390-612-10**).
20 mL sterile vials, each containing acyclovir sodium equivalent to 1000 mg of acyclovir, carton of 10. (**NDC 55390-613-20**).

Store between 15° to 25° C (59° to 77° F).

CAUTION - Federal law prohibits dispensing without prescription.

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April, 1997

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VARICELLA ZOSTER INFECTIONS

ZOSTER IN IMMUNOCOMPROMISED PATIENTS - 10 mg/kg infused at a constant rate over 1 hour, every 8 hours for 7 days in adult patients with normal renal function. In children under 12 years of age, equivalent plasma concentrations are attained by infusing 500 mg/m^2 at a constant rate over at least 1 hour, every 8 hours for 7 days. Obese patients should be dosed at 10 mg/kg (Ideal Body Weight). A maximum dose equivalent to 500 mg/m^2 every 8 hours should not be exceeded for any patient.

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25 - 50	100%	12
10 -25	100%	24
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April, 1997

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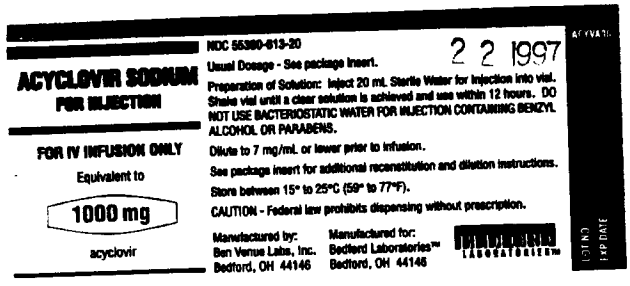
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Equivalent to
1000 mg
acyclovir
NDC 55390-613-20
Usual Dosage - See package insert.
2 2 1997
Preparation of Solution: Inject 20 mL Sterile Water for Injection into vial. Shake vial until a clear solution is achieved and use within 12 hours. DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.
Dilute to 7 mg/mL or lower prior to infusion.
See package insert for additional reconstitution and dilution instructions.
Store between 15° to 25°C (59° to 77°F).
CAUTION - Federal law prohibits dispensing without prescription.
Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146
Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
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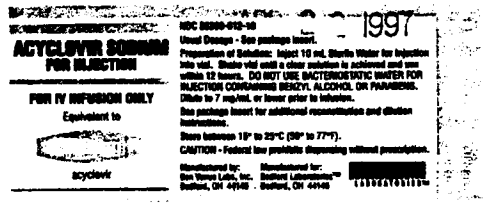
ACYCLOVIR SODIUM
FOR INJECTION
FOR IV INFUSION ONLY
Equivalent to
acyclovir
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1997

Prepared by
Mark Zarnstorff
Checked by

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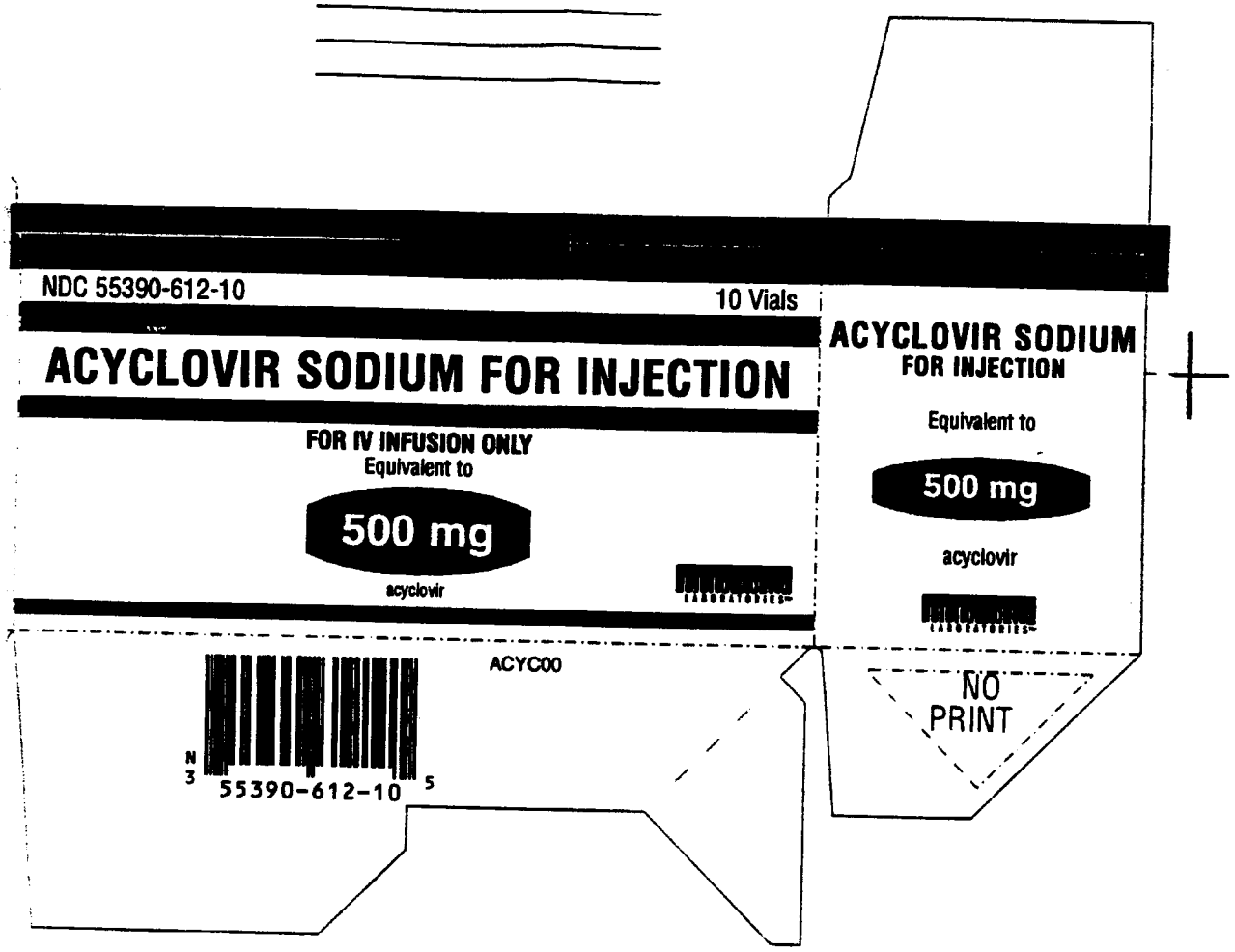

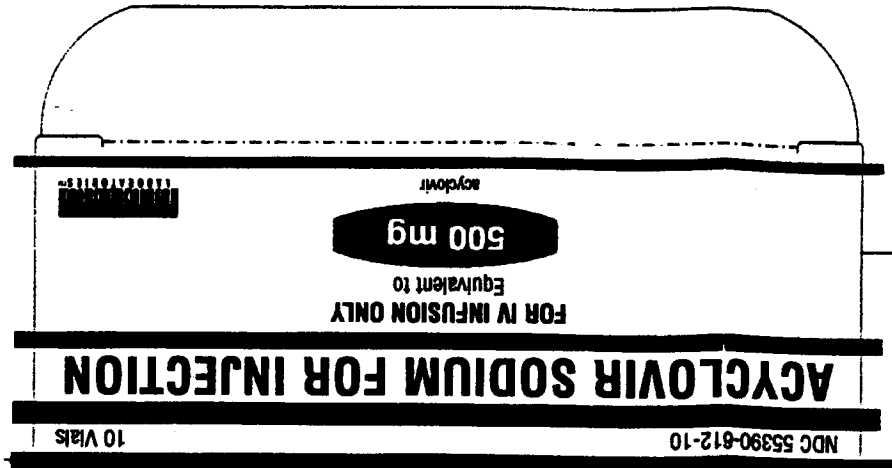

Usual Dosage - See package insert.

Preparation of Solution: Inject 10 mL Sterile Water for Injection into vial. Shake vial until a clear solution is achieved and use within 12 hours.
DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PARABENS.

Dilute to 7 mg/mL or lower prior to infusion.

See package insert for additional reconstitution and dilution instructions.

Store between 15° to 25°C (59° to 77°F).

CAUTION: Federal law prohibits dispensing without prescription.

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

LOT
EXP

ACYCLOVIR SODIUM
FOR INJECTION

Equivalent to

500 mg

acyclovir

NO PRINT

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Prepared by
Mark Zarnstorff
Checked by

[redacted]

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NDC 55390-613-20

l a clear solution is

L OR PARABENS.

ACYCLOVIR SODIUM
FOR INJECTION

Equivalent to

1000 mg

acyclovir

Manufactured by:
Ben Venue Labs, Inc.
Bedford, OH 44146

BEDFORD LABORATORIES™

[redacted]

ACYCLOVIR SODIU

FOR IV INFU

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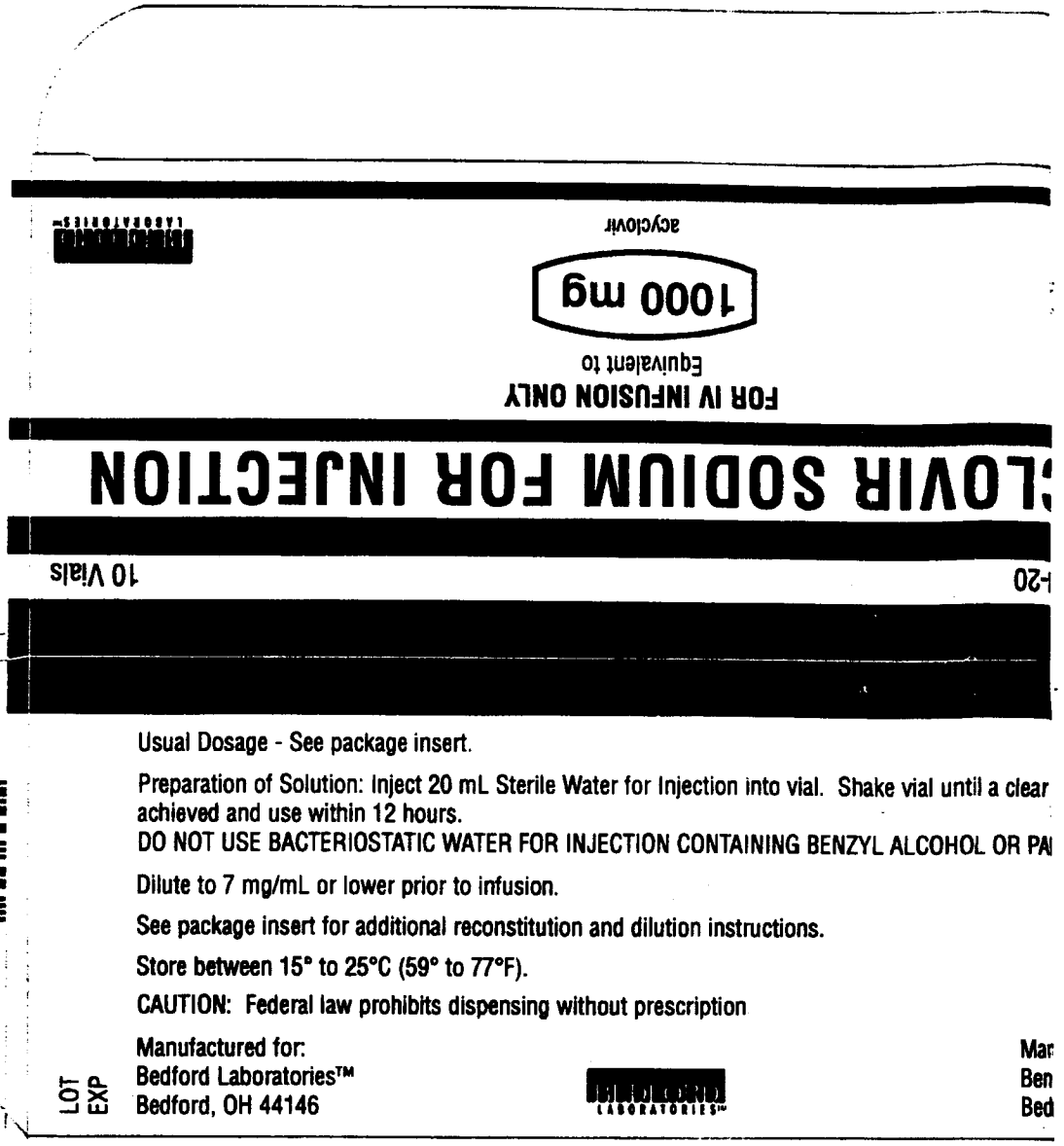

acyclovir
1000 mg
Equivalent to
FOR IV INFUSION ONLY
10 Vials
Usual Dosage - See package insert.
Preparation of Solution: Inject 20 mL Sterile Water for Injection into vial. Shake vial until a clear
achieved and use within 12 hours.
DO NOT USE BACTERIOSTATIC WATER FOR INJECTION CONTAINING BENZYL ALCOHOL OR PA
Dilute to 7 mg/mL or lower prior to infusion.
See package insert for additional reconstitution and dilution instructions.
Store between 15° to 25°C (59° to 77°F).
CAUTION: Federal law prohibits dispensing without prescription
Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
LOT
EXP

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074596

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-596 DRUG PRODUCT: Acyclovir Sodium FIRM: Bedford Labs

DOSAGE FORM: Powder for Injection STRENGTH: 500 mg & 1 g/vial

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable for all on 3/7/96.

BIO STUDY: The waiver of *in-vivo* bioequivalence study for 500 mg/ vial and 1 g/vial granted on 5/31/95.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Finish Dosage Form: Methodology suitable for regulatory purposes from Cincinnati District on 10/6/95.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol: Satisfactory.

Exp.Date: 24 months - 40°C, 75% R.H., 3 months, 1 lot each strength; and R.T. (27.5°C ± 2.5°C), 3 months, 1 lot each strength. Lot #686-13-0002 (1 g/vial), Lot #686-12-0002 (500 mg/vial).

Container/Closure systems are the same.

LABELING: Container: Satisfactory in FPL, C.Hoppes, 2/13/97
Carton: Satisfactory in FPL, C.Hoppes, 2/13/97
Insert: Satisfactory in Printers Proof, CHoppes, 2/13/97

STERILIZATION VALIDATION (IF APPLICABLE): [redacted] Confidential Commercial Info. Micro. acceptable on 2/2/96, JMcVey.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
[redacted] (Lot #686-13-0002 [100 mg/mL], Lot #686-13-0002 [1 g/vial], Lot #686-12-0002 [500 mg/vial]), source of NDS acceptable [redacted].

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS):
[redacted] (Lot #686-13-0002 [100 mg/mL], Lot #686-13-0002 [1 g/vial], Lot #686-12-0002 [500 mg/vial]).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY:
[redacted] process the same [redacted]

CHEMIST: Norman Gregory DATE: 2/21/97

SUPERVISOR: John Simmons, Ph.D. DATE: 2/21/97
Uvenkataram [redacted] 2/24/97
4-9-97

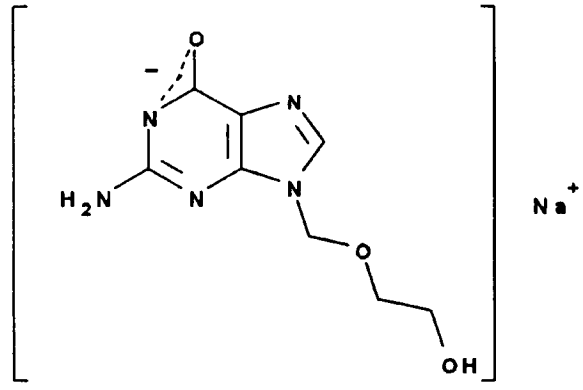
13. DOSAGE FORM
Powder for Injection
(lyophilized)

14. POTENCY
500 mg/vial & 1000 mg/vial

15. CHEMICAL NAME AND STRUCTURE

Acyclovir Sodium

$C_8H_{10}N_5NaO_3$; M.W. = 247.19



9-[(2-Hydroxyethoxy)methyl]guanine monosodium salt.
CAS [69657-51-8]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Chemistry, Labeling, Bio., DMF, EER and methods validation acceptable.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
2/21/97

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 74-596

3. NAME AND ADDRESS OF APPLICANT
Bedford Laboratories
Division of Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, OH 44146

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies, that to the best of their knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997 and there is no marketing exclusivity in effect for the listed drug.

Innovator: Burroughs Wellcome - Zovirax® Sterile Powder

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir Sodium
for Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
12/22/94 - Original.
8/16/95 - Response to 1st def. letter (chem., micro. & labeling).
1/25/96 - Response to Micro. phone memo.
5/22/96 - Response to 2nd def. letter (labeling).
1/27/97 - 90 day letter. Subject of this review.

FDA:
1/25/95 - Acknowledgment.
5/31/95 - Bio. review, waiver granted.
6/8/95 - 1st def. letter (chem., mirco. & labeling).
2/2/96 - Micro. review (acceptable).
4/26/96 - 2nd def. letter (labeling).
9/10/96 - 3rd review, tentative approval.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted] Confidential Commercial Info [redacted].

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074596

BIOEQUIVALENCE REVIEW(S)

MAY 31 1995

Acyclovir Sodium for Injection
Supplied as Lyophilized product
500 mg Acyclovir in 10 mL vial,
1000 mg Acyclovir in 20 mL vial,
Contents to be dissolved in sterile water to get 50 mg Acyclovir per mL in each case
ANDA # 74-596
Reviewer: Kuldeep R. Dhariwal
File name: 74596W.D94

Bedford Laboratories
Div. of Ben Venue Laboratories, Inc.
300 Northfield Road
Bedford, Ohio 44146

Submission Date:
December 22, 1994

REVIEW OF A WAIVER REQUEST

INTRODUCTION:

Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpesviruses. Innovator product is Zovirax® Sterile Powder manufactured by Burroughs Wellcome.

OBJECTIVE:

The firm requests a waiver of the requirement for in vivo bioavailability/bioequivalence study for Acyclovir Sodium for Injection- 500 mg/vial and 1000 mg/vial in accordance with 21 CFR 320.22 (b)(1).

FORMULATIONS:

Both test and reference products are supplied as lyophilized products to be reconstituted into a solution intended solely for intravenous administration. Both the products contain Acyclovir as active ingredient. Sodium hydroxide is used to convert Acyclovir to Acyclovir Sodium and adjust pH. The comparative formulations of the test and the reference products are as follows:

Ingredients	Amount	
	Test	Reference (Burroughs Wellcome)
Acyclovir	500 mg/vial or 1000 mg/vial	500 mg/vial or 1000 mg/vial
Sodium Hydroxide	used to convert Acyclovir to Acyclovir Sodium and adjust pH	

Water	used to prepare solution, removed during lyophilization process

COMMENTS:

1. The drug product is a lyophilized powder, that when reconstituted, is intended for intravenous administration.

2. The route of administration, dosage form, and amount of active ingredient are same in test and reference drug products.

3. Burroughs Wellcome has a patent on Zovirax® Sterile Powder which will expire on April 22, 1997.

RECOMMENDATION:

The Division of Bioequivalence agrees that the information submitted by Bedford Laboratories demonstrates that Acyclovir Sodium for Injection, 500 mg/vial and 1000 mg/vial falls under 21 CFR Section 320.22 (b)(1) of the Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study for 500 mg/vial and 1000 mg/vial, Injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Zovirax® Sterile Powder for Intravenous administration, 500 mg/vial and 1000 mg/vial manufactured by Burroughs Wellcome.

[redacted]
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED R.PATNAIK
FT INITIALED R.PATNAIK [redacted] Date 5/30/95

Concur: [redacted] Date 5/31/95
[redacted]th Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 74-596 (Original), HFD-600 (Hare), HFD-630, HFD-655 (Patnaik, Dhariwal), Drug File, Division File